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Client Alert

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FDA Initiates Expedited Access Pathway Program for Medical Devices via Final Guidance Document

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The U.S. Food and Drug Administration (FDA) initiated an Expedited Access Pathway (EAP) Program, effective April 15, 2015, for certain medical devices that are subject to premarket approval applications (PMAs) or *de novo* requests. FDA formally established the EAP program through a final guidance document titled "Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions" (hereafter, EAP Guidance), issued on April 13, 2015.[1]

The EAP Guidance states that the EAP program is based in part on the expedited review and approval programs for new drug products that are intended to address unmet medical needs in the treatment of serious or life-threatening conditions. The development of the EAP program is also informed by the Center for Devices and Radiological Health's Innovations Pathway, piloted in 2011 and intended to facilitate the development and expedite the review of breakthrough technologies. The EAP framework, adopted for PMA and *de novo* devices, works in conjunction with FDA's existing processes for making benefit-risk determinations for medical devices and authorities for requiring postmarket data collection and reporting. The EAP Guidance explains how FDA applies these existing processes through the EAP program to "help patients have more timely access to [certain PMA and *de novo* devices] by expediting their development, assessment, and review, while preserving the statutory standard of reasonable assurance of safety and effectiveness for premarket approval . . . ."[2]

The EAP Guidance describes the criteria for devices' eligibility for EAP designation; the benefit-risk determinations that FDA makes regarding devices subject to the EAP program; the features and benefits of the EAP Program; and the process for requesting EAP designation.[3]

Features of the EAP Program for PMA and *De Novo* Devices

Sponsors of devices that receive EAP designation and proceed through the EAP program can expect to receive earlier and more interactive engagement with FDA. FDA also plans to involve senior management and/or a case manager in the EAP review process when appropriate and when resources permit. Additionally, EAP premarket submissions for

PMA devices receive priority review status under section 515(d)(5) of the federal Food, Drug, and Cosmetic Act (FDCA).[4] For *de novo* requests, FDA also plans to expedite its review of the pre-market submission and to make a determination in a shorter timeframe than the statutory 120-day deadline for traditional *de novo* requests.

Eligibility for EAP Review

FDA based the three criteria for eligibility for EAP review on the existing statutory criteria for priority review, contained in FDCA section 515(d)(5). All three criteria must be met for a device to receive EAP designation. FDA has the final decision of whether a device is eligible for review through the EAP program. The first EAP criterion is that the device is **intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition**. Under this first prong, FDA will consider for EAP designation devices that "are intended to have a positive effect on a ***serious aspect*** of the life-threatening or irreversibly debilitating disease or condition."[5] " FDA also intends to consider devices that have a specific intended use to cure, diagnose, mitigate, or prevent a life-threatening or irreversibly debilitating disease or condition in a population or subpopulation that meets the conditions for unmet medical need."[6] A "life-threatening" disease or condition is one "for which the likelihood of death is high unless the course of the disease is interrupted . . . ."[7] Further, a disease or condition is "irreversibly debilitating" if it is "associated with morbidity that has substantial impact on day-to-day functioning . . . ."[8] Such diseases or conditions generally are persistent, recurrent, or progress to a more serious disease or condition.

The second criterion is that the device **address an unmet need**. An unmet medical need "is a condition [in a population or subpopulation] whose treatment or diagnosis is not addressed adequately by an available therapy or diagnostic."[9] There are four ways that a device could address an unmet need. The EAP Guidance gives examples of each:

- *No appropriate alternative treatment or means of diagnosis*. An "appropriate alternative" is a device that is approved or cleared for the same indication and is "relevant" to the current standard of care in the United States for the indication. However, FDA notes that a device that is used off-label for the indication at issue may be considered an appropriate alternative if it is supported by compelling evidence and is the standard of care in the United States.

- *Breakthrough technology that provides a clinically meaningful advantage over existing legally marketed technology*.

- *Significant, clinically meaningful advantages over existing legally marketed alternatives.* Devices that address an unmet need by providing a significant, clinically meaningful advantage "ha[ve] the potential to cure, provide a clinically important earlier or more accurate diagnosis or treatment monitoring, or offer important therapeutic or preventative advantages in safety and/or effectiveness over existing alternatives."[10] FDA provides as examples devices with superior effectiveness outcomes or substantially less risk than existing treatments. FDA also considers devices that present solutions to known, important shortcomings of existing treatments or that benefit patients who cannot tolerate current treatments.[11]

- *Best interest of patients*. This final category of unmet medical need is a catch-all category intended to apply to devices or indications for "a [disease or] condition whose treatment or diagnosis is not addressed adequately by an available therapy or diagnostic" and that "provide[] a specific public health benefit or addresses an unmet medical need of a well-defined patient population."[12] The EAP Guidance provides several examples of ways that a device could meet the unmet medical need criterion and potentially be eligible for the EAP program by being in the best interest of patients.

The third, and final, criterion for EAP eligibility is that the **sponsor submits an acceptable draft Data Development Plan.** The Data Development Plan, explained in detail in Attachment 2 of the EAP Guidance, is a key feature of the EAP program and it describes the data, both clinical and nonclinical, that the sponsor intends to collect in the premarket time period for EAP *de novo* devices[13] and in both the pre- and post-market time periods for EAP PMA devices. The Data Development Plan also describes the analysis plan for all data that will be collected and contains an estimated timeline for device development and marketing. For EAP PMA devices that utilize postmarket data collection, the Data Development Plan also provides a rationale for using postmarket data and the timeline and plan for data collection. The sponsor submits the draft Data Development Plan as part of the request for EAP designation and, if the device is accepted into the EAP program, FDA and the sponsor collaboratively refine and finalize the Data Development Plan during the pre-approval period. It is important to note that the FDA requests that "[s]tudy endpoints should prespecify the minimum clinically meaningful effect."[14]

Once FDA grants a device an EAP designation permitting it to proceed through the EAP program, the Agency will only revoke the EAP designation if the FDA determines that the information submitted in support of the request contained false information or statements or material omissions, or if the Agency determines that the device no longer meets the criteria for EAP designation. FDA will not revoke EAP designation, once granted, solely because a similar device is approved or receives a *de novo* marketing authorization

Additional Features of EAP for PMA Devices

In addition to early and increased interactive communication with FDA and priority review, FDA has indicated that it may be more willing to shift data collection to the post-approval timeframe for PMA devices reviewed through EAP program, rather than requiring all clinical data to be collected prior to PMA approval. The EAP Guidance explains that FDA may accept a greater degree of uncertainty in an EAP device's benefit-risk profile than it would for a PMA device that does not meet the EAP criteria if that uncertainty is "sufficiently balanced by other factors, including the probable benefits for patients to have earlier access to EAP Devices . . . and adequate postmarket controls . . . ."[15] Section III.C of the EAP Guidance provides ten factors that FDA will consider when deciding whether to accept greater uncertainty about a device's benefit-risk profile.

Because FDA recognizes the potential public health benefit from EAP devices, FDA intends to permit the use of certain more flexible types of clinical evidence in support of a PMA for an EAP device. The EAP Guidance provides detailed information about, and examples, of these types of clinical evidence, which include:

- Intermediate and surrogate endpoints that are reasonably likely to predict clinical benefit. When such endpoints are used, FDA plans to require postmarket confirmatory data as a condition of approval.

- Two-phase studies in which one study is planned to provide initial evidence of safety and efficacy in a premarket phase with confirmatory data obtained in a postmarket phase.

- For in vitro diagnostic devices (IVDs), alternative experimental designs that demonstrate the analytical and clinical validity of an IVD without clinical performance measures. Such experimental designs include the use of banked samples or contrived samples.

- Other sources of clinical evidence, for example, registry data.

Under the EAP program, FDA may also allow PMA sponsors to submit less manufacturing information in an application than the Agency would traditionally require. Further, in certain circumstances, the Agency may approve a PMA for an EAP device without conducting a pre-approval inspection of the manufacturing facility. Whether

FDA will forego the pre-approval inspection depends on the timing and outcome of the facility's most recent inspection, as described in section III.E of the EAP Guidance.

The Tradeoff for PMA Devices – Conditions of Approval and Post-Market Actions

In exchange for accepting a greater level of uncertainty about a device's benefit-risk profile, FDA may exercise its authority to condition the approval of EAP PMA devices on postmarket data collection including continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of approved EAP devices. FDA may also choose to impose conditions of approval on the device's labeling. These potential postmarket requirements are detailed in Section III.F of the EAP Guidance.

Potential Implications of the EAP Program

Manufacturers should carefully consider the potential benefits to be gained from participating in the EAP program (e.g., intermediate/surrogate endpoints, less pre-market clinical data, fewer pre-approval manufacturing requirements) against the potential risks associated with pre-specifying the minimal clinically meaningful effect (i.e., study success criteria) and conditioning approval on postmarket studies. For a novel device or new indication, it may be difficult to define success without data to weigh benefits and risks. Further, in the EAP Guidance, FDA notes that it may withdraw PMA approval if a manufacturer fails to complete postmarket requirements. In our experience, it becomes more difficult to convince physicians to enroll patients in postmarket studies once a device is approved or cleared or otherwise available for clinical use for any purpose. FDA does state in the EAP Guidance that it may permit the use of registry data to meet the requirements of a post-approval study; however, the Agency may not necessarily allow the use of registries in all cases. FDA rarely, if ever, has exercised its authority to withdraw PMA approval due to noncompliance with postmarket data collection requirements ; however, the EAP Guidance suggests FDA may more rigorously enforce these requirements for devices reviewed through the EAP program.

Manufacturers may also wish to consider the implications for CMS coverage and reimbursement of expedited approval that relies more heavily on post-market data to confirm the safety and effectiveness of a device. Approval through the EAP program provides no assurance that the data supporting premarket approval will be deemed to be sufficient to meet the CMS standard of "reasonable and necessary" for Medicare beneficiaries.

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King & Spalding will continue to monitor FDA's policy, guidance, and regulations regarding the EAP program and medical device approvals, clearances, and clinical data more broadly. Please let us know if you have any questions about the application of FDA's new EAP program.

[1] Food & Drug Admin., Center for Devices & Radiological Health and Center for Biologics Evaluation and Research, "Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions" (hereafter, EAP Guidance), Apr. 13, 2015, *available at*

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393978.pdf. The EAP Guidance was announced in the Federal Register, 80 Fed. Reg. 19669 (Apr. 13, 2015).
[2] 80 Fed. Reg. at 19669.
[3] A complementary, but separate, final guidance also issued by FDA on April 13, 2015, describes the Agency's approach to balancing pre- and post-market data collection for PMA devices. *See* Food & Drug Admin., Center for Devices & Radiological Health and Center for Biologics Evaluation and Research, "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval" (hereafter, Data Collection Guidance), Apr. 13, 2015, *available at* http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393994.pdf. This guidance contains some of the same concepts as the EAP Guidance with respect to shifting some data collection requirements to the post-approval timeframe and may be helpful to consider for certain PMA devices that are not eligible for the EAP program.
[4] 21 U.S.C. § 360e(d)(5); *see also* Food & Drug Admin., Center for Devices & Radiological Health and Center for Biologics Evaluation and Research, "Priority Review of Premarket Submissions for Devices," May 17, 2013, *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089698.pdf.
[5] *EAP Guidance* at p. 12 (emphasis added).
[6] *Id.*
[7] *Id.* at 12–13.
[8] *Id.* at 13.
[9] *Id.* at 16.
[10] *Id.* at 15.
[11] *Id.*
[12] *Id.* at 16.
[13] Postmarket benefits are not available to *de novo* devices because of the risk that an EAP *de novo* device is used as a predicate device for future 510(k) devices, only to later be found not safe or effective based on postmarket data. *Id.* at 9.
[14] *Id.* at 21.
[15] *Id.* at 20.